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SYNTHETIC PERIPLOGENIN

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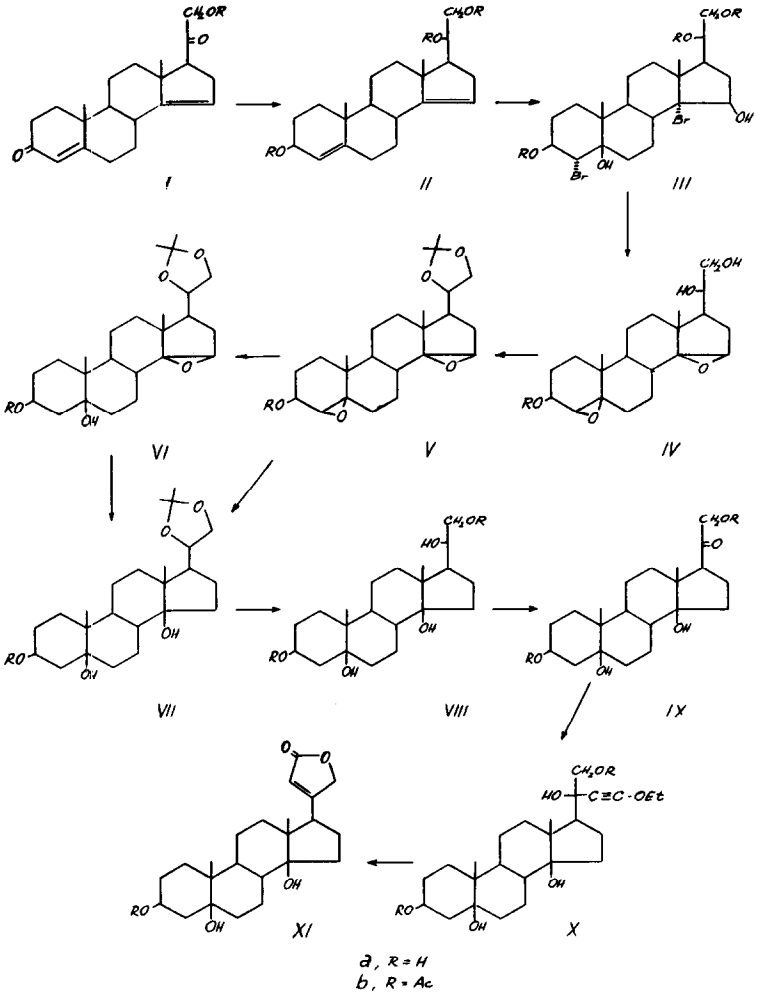
The first synthesis of a cardioactive steroidal aglycone (digitoxigenin) was recently reported[1].

We now wish to record a simpler synthesis, starting from readily available steroids, of the more complex aglycone periplogenin [2,3] (XIa) (19-desoxostrophanthidin), found in several species of the Strophanthus genus[4], and which possesses two tertiary hydroxyl groups (5β,14β), a common feature of the most potent cardiotonic constituents[5]. 14-Dehydro-D.O.C.A. (Ib)[6,7], obtained by dehydrating the readily available 14α-hydroxy-D.O.C.A.[8] or by chemical[9] or microbiological[10] hydroxylation in position 21 of 14-dehydroprogesterone[11], was reduced with $LiAlH_4$ in tetrahydrofuran to the triol IIa[m.p. 133-136°,$[\alpha]_D$ + 63° (dioxane)] and acetylated to the triacetate IIb (m.p. 129-130°,$[\alpha]_D$ + 34°]. Addition of HOBr to IIb (N-bromoacetamide in acid aqueous dioxane) provided the bis-bromohydrin IIIb[m.p. 138-139°,$[\alpha]_D$ + 73°]. The position of the bromine atoms is consistent with that found in analogous reactions involving separately the 4,5 and 14,15 double bonds.[10,12,13]

Treatment of IIIb with methanolic KOH[12] gave the bis-epoxide IVa [m.p. 181-183°,$[\alpha]_D$ - 21.5° converted to the acetonide Va[m.p. 192-195°, $[\alpha]_D$ + 17.5° (acetone)] with acetone at room temperature in presence of anhydrous $CuSO_4$. Selective opening of the 4,5-epoxide in Va was effected by $LiAlH_4$ in tetrahydrofuran at room temperature to give the epoxydiol VIa [m.p. 190-192°,$[\alpha]_D$ + 43°], acetylated to the acetate VIb(m.p. 161-163°,



a, R = H
b, R = Ac

$[\alpha]_D$ + 58°] or further reduced by $LiAlH_4$ in boiling tetrahydrofuran to the triol VIIa[m.p. 201-203°, $[\alpha]_D$ + 33° (acetone)]. The latter compound could be obtained directly from Va with $LiAlH_4$ in refluxing tetrahydrofuran. Acetylation with acetic anhydride in pyridine gave the acetate VIIb[m.p. 154-156°, $[\alpha]_D$ + 46.5°] which was hydrolyzed to the tetrol VIIIa[m.p. 207-209°, $[\alpha]_D$ + 30°] by room temperature treatment with 0.05 n H_2SO_4 in methanol and selectively acetylated with acetic anhydride in dioxane and pyridine[14] to the diacetate VIIIb[m.p. 155-156°, $[\alpha]_D$ + 31°]. Chromic acid oxidation in dimethylformamide[15] afforded the 20-ketone IXb[m.p. 151-152°, $[\alpha]_D$ + 70°] previously[14] obtained by degrading natural periplogenin. Reaction of IXb with lithium ethoxyacetylide in benzene-ether gave the acetylenic carbinol Xb (not isolated, ν_{max} 2250 cm^{-1}, -C≡C-, 1725 and 1225 cm^{-1}, acetate). Treatment of Xb with 1 n HCl in methanol at room temperature for 16 hours gave periplogenin XIa[m.p. 135-140° from MeOH-H_2O[16], after drying m.p. 235°], purified through chromatography on silica and identical with the natural aglycone[17,18].

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